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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/185,243	11/03/98	TSANG T	15907-0016

HM22/0710
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EXAMINER	
KERR, J	
ART UNIT	**PAPER NUMBER**
1633	15

DATE MAILED: 07/10/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Advisory Action

Application No.	Applicant(s)
09/185,243	Tsang et al.
Examiner	**Art Unit**
Janet M. Kerr	1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED *Jul 2, 2001* FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid the abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

THE PERIOD FOR REPLY [check only a) or b)]

a) ☐ The period for reply expires _____ months from the mailing date of the final rejection.

b) ☐ In view of the early submission of the proposed reply (within two months as set forth in MPEP § 706.07 (f)), the period for reply expires on the mailing date of this Advisory Action, OR continues to run from the mailing date of the final rejection, whichever is later. In no event, however, will the statutory period for the reply expire later than SIX MONTHS from the mailing date of the final rejection.

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *Jul 2, 2001*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will be entered upon the timely submission of a Notice of Appeal and Appeal Brief with requisite fees.

3. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search. (See NOTE below);

   (b) ☒ they raise the issue of new matter. (See NOTE below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: *see attached.*

4. ☒ Applicant's reply has overcome the following rejection(s):
   none

5. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claim(s).

6. ☒ The a) ☒ affidavit, b) ☐ exhibit, or c) ☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because:
   see attached.

7. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

8. ☒ For purposes of Appeal, the status of the claim(s) is as follows (see attached written explanation, if any):

   Claim(s) allowed: *none*

   Claim(s) objected to: *none*

   Claim(s) rejected: *1, 5-7, 9-18, 20-26, 33, 35-39, 41, and 43-46*

9. ☐ The proposed drawing correction filed on _____ a) ☐ has b) ☐ has not been approved by the Examiner.

10. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

11. ☐ Other:

Deborah Clark

DEBORAH J. R. CLARK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Response to Amendment Submitted After Final

The amendment submitted 7/2/01 has not been entered since it raises issues of new matter issues. For example, the replacement of Table 4 results in alterations in the amount of IL-2 expressed by the vectors. While it is asserted that the specification supports these changes, applicants have not specifically indicated where support for these new values is found in the specification. In addition, the amended claims would require a new search and consideration as deletion of the activation temperature ranges broadens the scope of the claimed invention.

Applicants' arguments directed to the amended claims have been noted but are moot as the amendment has not been entered.

The declaration under 37 CFR 1.132 filed 7/2/01 is insufficient to overcome the 35 U.S.C. 102 or 35 U.S.C. 103 rejections of claims 1, 5-8, 10-16, and 39-46 based upon the reference of Bromley *et al.* as set forth in the previous Office actions (Paper Nos. 10 and 12).

It is asserted that while the reference of Bromley *et al.* discusses/claims a method of producing proteins encoded by genes of interest placed under the expression control of a promoter regulated by an endogenous activation factor in which "hybrid genes" are carried by two independent or only one transfer vector, the reference does not provide guidance as to how to construct a dual gene vector, and provides no working examples of cloning/transfecting a dual gene vector (see paragraph 2 of the declaration of David T. Harris).

It is argued that the inventors of the instant application were the first to publish the dual gene amplifier vectors, and factors such as vector size, the use of HIV 1 LTR or HIV 2 LTR, the effects of adding more than one transcription unit to the same vector, and the relative orientation of the transcription units were taken into consideration when constructing the amplifier vector. It is asserted that the construction of the amplifier vector involved much more than ligating transcriptional units together. It is argued that positions of the transcriptional units and promoters, and the size of the expression vector are factors to be considered for appropriate transfection and expression (see paragraph 3 of the declaration). By constructing ten different

dual gene expression vectors using various combinations of the components in the transcriptional units, it was determined that HIV 2 promoter-based amplifier constructs produced 28 times more secreted IL-2 than the CMV promoter control and three times higher than those obtained with the HIV 1 promoter-based amplifier constructs. It was further determined that the augmented activity of the amplifier constructs is dependent on the presence of the tat gene, and that the addition of the SV40 promoter significantly increased expression levels. It is argued that placing the transcriptional units in the "wrong" orientation completely abolished the augmented expression, which provides support for declarant Harris' argument that the vectors of the instant application are constructed according to a specific strategy and any small alteration may lead to entirely different results (see paragraph 3 of the declaration).

Declarant Harris argues unexpectedly high levels of gene expression using the vectors f12, 007, X14, and Y15 (see paragraph 4 of the declaration). It is argued that the high levels of expression obtained with the vectors disclosed in the instant application are unique and potentially useful as the use of expression vectors in cytokine-mediated gene therapy requires extremely high levels of cytokine gene expression in order to be clinically effective (see paragraph 4 of the declaration).

The arguments presented by Declarant Harris have been carefully considered but are not deemed persuasive for the following reasons:

Although it is argued that constructing the amplifying vector requires careful consideration with respect to the types of elements incorporated in the vector, the placement and orientation of the transcriptional units, the placement of the promoters, the enhanced expression levels of vectors comprising (1) the HIV 2 promoter relative to the HIV 1 promoter, (2) the presence of the tat gene, and (3) the addition of the SV40 promoter significantly increased expression levels such that the disclosed constructs have a much higher level of expression compared to vectors known in the art, i.e., results which are unexpected, it should be noted that only dependent claims 9 and 43 recite the limitations of an HIV promoter and the tat gene; claims 13 and 45 recite the

limitation that an IRE is present in the construct (the only other structural element recited in a claim other than a promoter and the gene(s) of interest. There are no claims which recite the presence of the SV40 promoter. In addition, there are no limitations reciting orientation of transcriptional units, promoter proximities, or size limitations. Note also that claim 18 does not require one vector comprising two promoters, one operatively linked to a gene encoding a transactivating factor and the other operatively linked to a gene of interest. With regard to the unexpectedly high levels of gene expression using the vectors f12, 007, X14, and Y15, it is noted that there are no claims directed to these vectors. With regard to the reference of Tsang *et al.* presented as Exhibit B, the reference teaches specific elements, orientations of the elements, and placement of the elements within the vector (see, e.g., Figure 1, page 4, under "Results", and page 5, left column, third full paragraph). There is no recitation of such features in applicants' claimed invention. Declarant Harris is arguing limitations which are not recited in the claims (with the exception of those noted above) and therefore, the arguments are not commensurate in scope with the claimed invention.

With regard to the reference of Bromley *et al.*, as set forth in the previous Office actions, Bromley *et al.* teach that the hybrid genes can be part of one or separate vectors (see pages 3-6 of Bromley *et al.* for teachings of the construct components). There is no distinct between the components of the taught vector and the components of the claimed vector (see claims 1-7, 9-12, 14, 16, 39-41, 43, 44, and 46). Thus, there is no objective evidence as to why the constructs of Bromley *et al.* would not be capable of efficient transfection and expression compared to the claimed vector(s) when the taught vectors and the claimed vectors have the same structural features.

For the reasons of record and the reasons set forth above, the rejections are maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to Deborah Clark, Supervisory Primary

Examiner of Art Unit 1633, at (703) 305-4051. Any administrative or procedural questions should be directed to Kimberly Davis, Patent Analyst, at (703) 305-3015. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401.

Janet M. Kerr, Ph.D.
Art Unit 1633
Group 1600